Cholesterol, CV risk & statins in Older Persons (OP: 75+)

(an evidence-based approach)

Prof. Benoit Boland
Geriatric Medicine,
UCL-Brussels

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CVRisk & Cholesterol management in the Elderly (75+)

- In the elderly, pyramid (4 faces)
  1. Ageing & Health
  2. Ageing & Morbi-mortality
  3. Ageing & CVRisk
  4. Ageing & Lipids
- Complex decision making (at all ages !)
  EBM approach

1. Older age & Health

- GOALS in OP
  - To decrease consequences of diseases
  - To prolong independence
  - To prevent social isolation
- MEANS
  - ↑ nutrition (→ weight)
  - ↑ physical activity (→ muscle)
  - ↑ interactions (→ social life)
  - *± ↓ cholesterol ?* *(→ ? reason ?)*

2. Older age & Morbi-mortality

- First cause of morbi-mortality = CVD
  - C²VD (Coronaro&Cerebro Vascular Diseases)
- Burden : non-C²VD > C²VD
  - Alzheimer, cancers, infections, …
- Medical decisions (EBM) in older persons
  - Life expectancy ?
  - « Quality of life » ?
  - Personal wishes & preferences ?

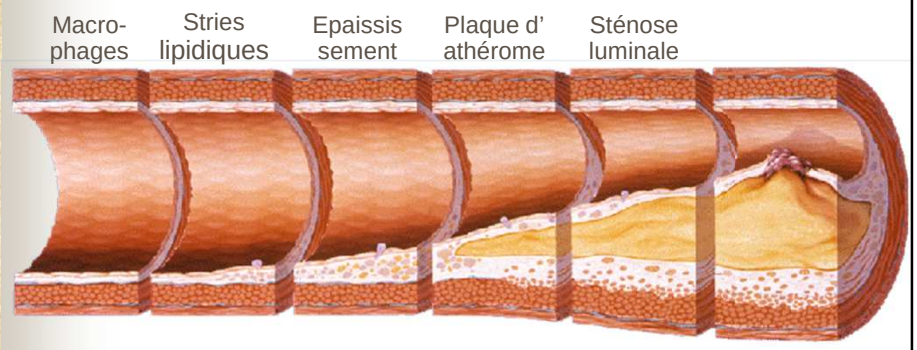
3. Older age & CVRisk

- CVRisk : ↑ with age (exponential)
  - CVRisk definition = absolute 10 years risk of acute event (MI or stroke; fatal or not)
- Coronary disease : very frequent in OP
  - observed in 70% of 70+ (post-mortem analyses)
  - men > women
- Gender difference (~10 yrs)
  - half of longevity differential
  - sex ratio: progressive ↑ with age
    persons 80+ : 3 w / 1 m

4. Older age & Lipids

- Blood changes with ageing
  - ↓ Total Chol. & Chol-LDL
  - ↔ HDL-Chol
- Effects of diseases
  - Acute: inflammation
  - Chronic: malnutrition
- Effects of statins
- Association Cholesterol → CVD

ATHéro matose –> thrombose –> sclérose…



0 – 25 ans	25 – 50 ans	50 à 75 ans	
	bouillie	sclérose	thrombose

B BOLAND, PCV & PA 75+

Science

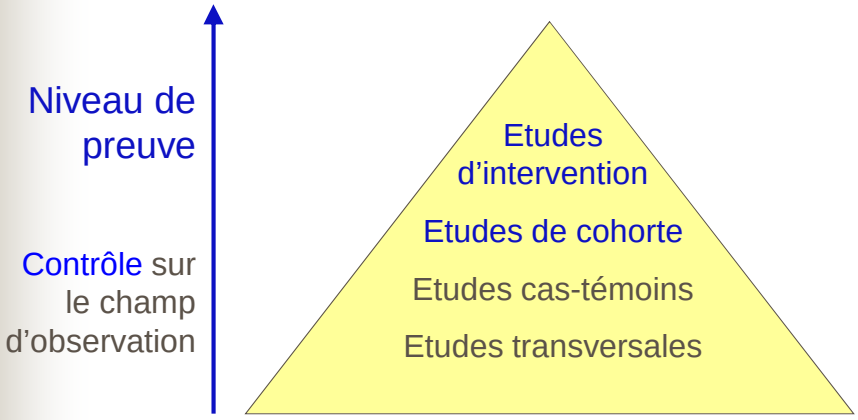
- Physiopathologie « fondamentale »
- Observations
- Connaissances théoriques
- Avis d'experts internationaux
- Autorité : guidelines

ScienceBM *vs.* EvidenceBM :

- Physiopathologie « fondamentale »
- Observations non-systématiques
- Connaissances théoriques
- Avis d'experts
- Autorité acceptée

- Physiopathologie « insuffisante »
- Observations systématiques
- Démonstrations concrètes (preuves)
- Evaluation des données
- Autorité contestée

EBM & hiérarchie des différents types d'études cliniques



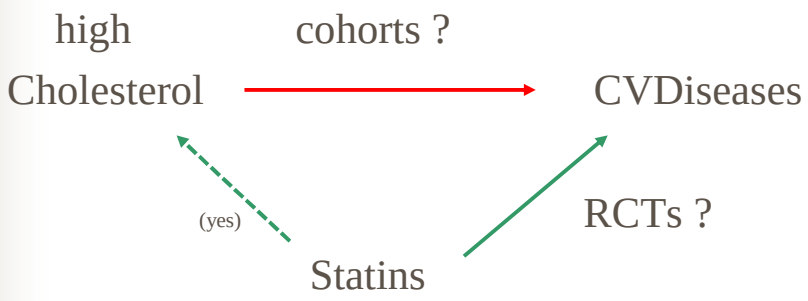
Two central geriatric questions …

1. Is cholesterol a CV risk factor at age ≥ 75 years ?

2. How much is a statin appropriate at age ≥ 75 years ?

   → clinical benefit *vs.* harm

evidence for links in OP (75+) ?



1. In older persons (75+), is cholesterol a CV Risk Factor ..?

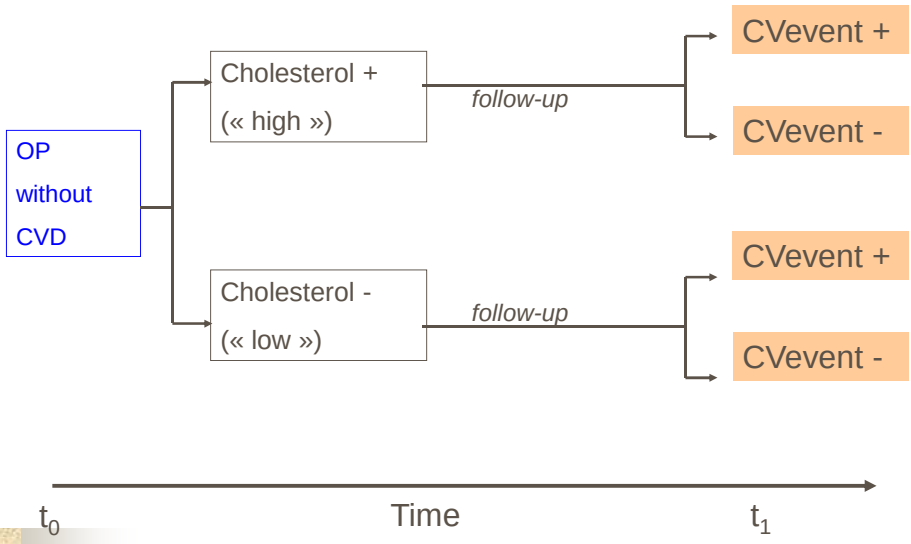
- Classical approach (physiopathology)
- EBM approach (etiology)
  - Question: « P E O » (causative arguments)
  - Search for valid sources of information :
    - Hierarchy: (SR) > **cohorts** > RCT_control arm
  - Critical appraisal
    - *PROSPER, Lancet 2002* *70+*
    - *CV HEALTH study, JAGS 2004* *65+*
    - *LEIDEN study, Lancet 1997* *85+*

Cholesterol in OP70+ is not a CV risk factor (MI or Stroke)

- PROSPER study (RCT, **control arm**)
  Lancet 2002; 360: 1623-1630
- Control arm, ~2.900 persons aged 70 – 82 yrs
  - mean age 75 yrs; with ou w/o CV event
- Events : 3.2 yrs of f/up
  - MI: NO association with LDL-C, but with HDL-C
  - Stroke: weak association with Chol.
  - CV Mortality : NO association with Chol.

→ Chol. does not predict CV events in 75 (± 5) yrs

Cohort study : design



Cholesterol in 65+
is not a CV risk factor (MI or Stroke)

- CV HEALTH study (cohort, 7.5 yrs of f/up)
  JAGS 2004; 52: 1639-47
- 4.885 persons 65+ (mean 73 yrs), free of CVD
- Events : 436 MIs, 332 Strokes, 1096 deaths
  - MInfarct : NO association with Chol.
  - Stroke : weak association with Chol.
  - CV Mortality : NO association with Chol.

→ Chol. does not predict CV events in 73 (± 8) yrs

Cholesterol in OP85+ is not a factor for CV risk or death

- **LEIDEN** study (Cohort, 10 yrs: 1987–1996)
  - Lancet 1997; 350: 1119-1123
- All inhabitants aged > 85+ (born 1883–1901)
  - n=750; mean age 89 yrs; ~90% free of CVD at baseline
- Mortality: 10 yrs of f/up
  - high : 90% at 10 years
  - elevated cholesterol (260 mg/dl)
    - is not a RF for CV mortality
    - is a PF for non CV mortality (infection, cancer)

→ Chol. does not predict CV mortality in 89 (±10) yrs

BASELINE CHARACTERISTICS, year 1987

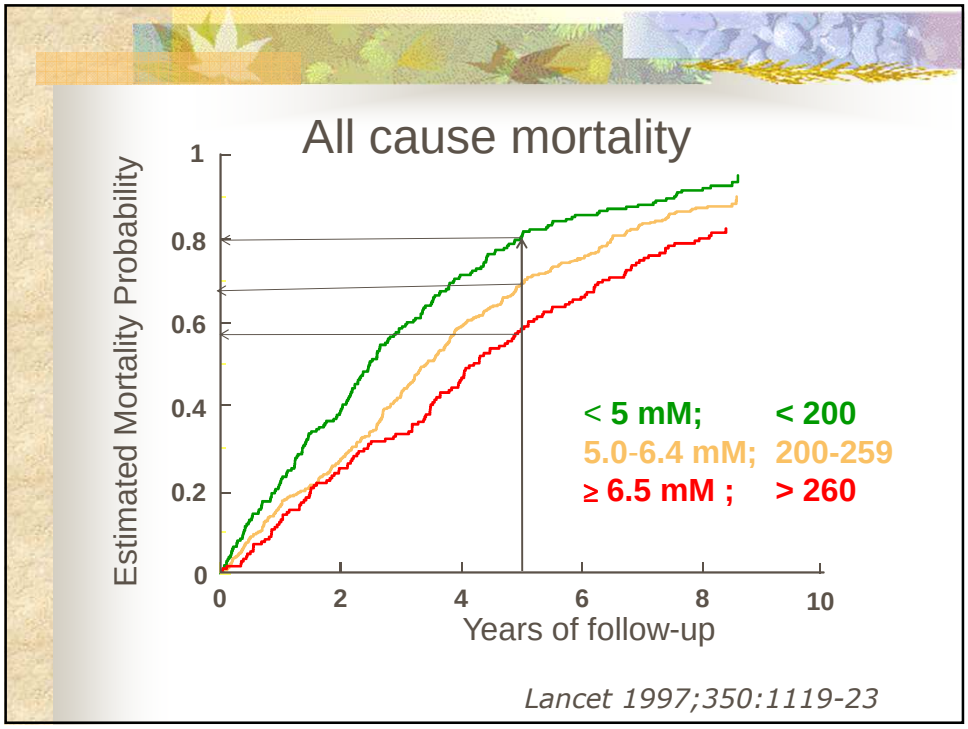
Characteristics	N=724
Male/Female	200/524
Year of birth	1883-1901
Median age in years (range)	89 (85 – 103)
Total cholesterol	
≥ 6.5 mmol/L	171 (24%)
5.0 – 6.4 mmol/L	350 (48%)
<5.0 mmol/L	203 (28%)
Cardiovascular risk	
RR diastolic (>90 mmHg)	204 (32%)
RR systolic (>160 mmHg)	285 (44%)
Diabetes	89 (12%)
Present smoking	117 (17%)
Previous myocardial infarction	58 (9%)
Previous cerebrovascular acc.	19 (3%)

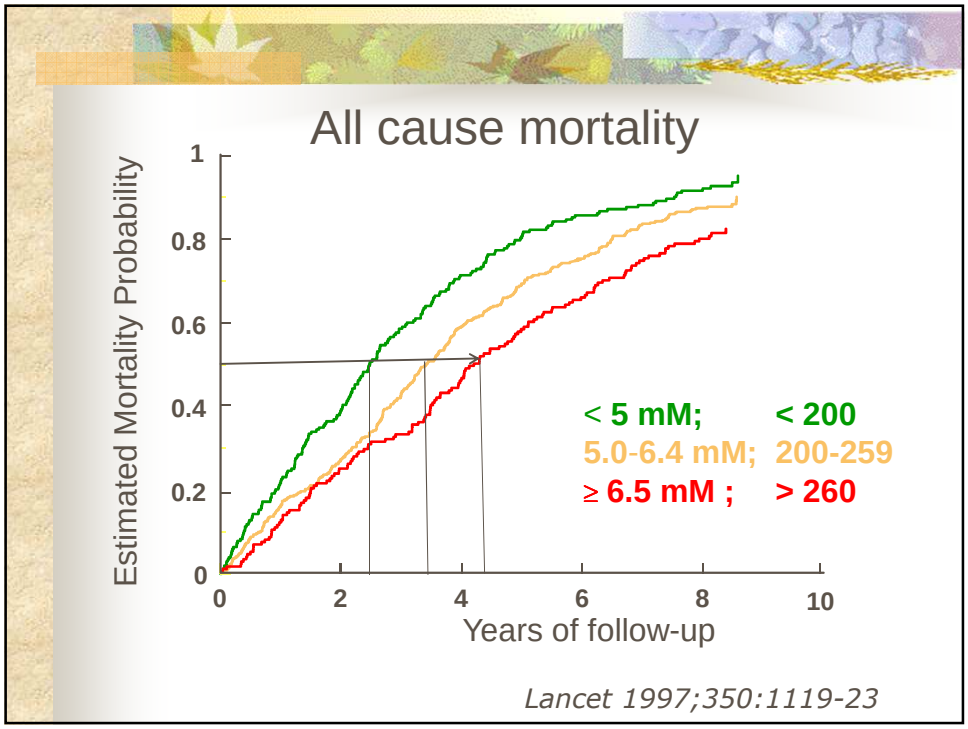
Weverling-Rijnsburger AW, *Lancet 1997;350:1119-23*

10 - year mortality risks adjusted for various determinants

Total cholesterol	Subjects (no)	Mortality risk		
		Unadjusted	Adjusted age and sex	Adjusted age, sex and risk factors
≥ 6.5 mmol/L	171	0.56 (0.45-0.69)	0.62 (0.49-0.77)	0.64 (0.50-0.82)
5.0- 6.4 mmol/L	350	0.72 (0.60-0.86)	0.78 (0.65-0.94)	0.81 (0.66-1.01)
< 5.0 mmol/L	203	1.00	1.00	1.00

Lancet 1997;350:1119-23


All cause mortality
Estimated Mortality Probability
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Years of follow-up
< 5 mM; < 200
5.0-6.4 mM; 200-259
≥ 6.5 mM ; > 260
Lancet 1997;350:1119-23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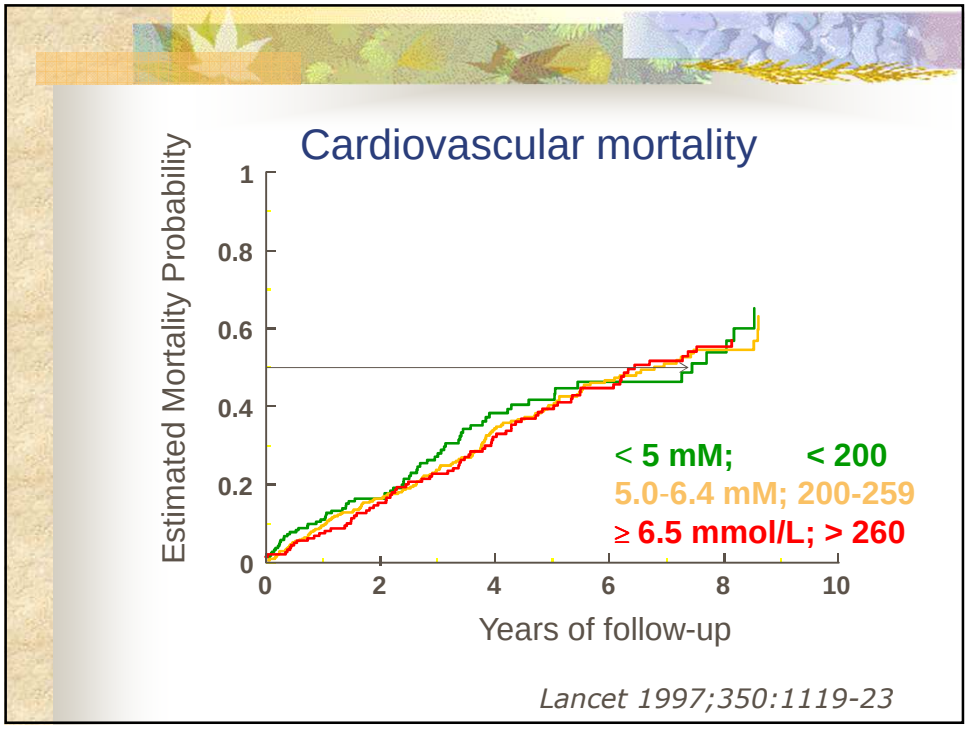
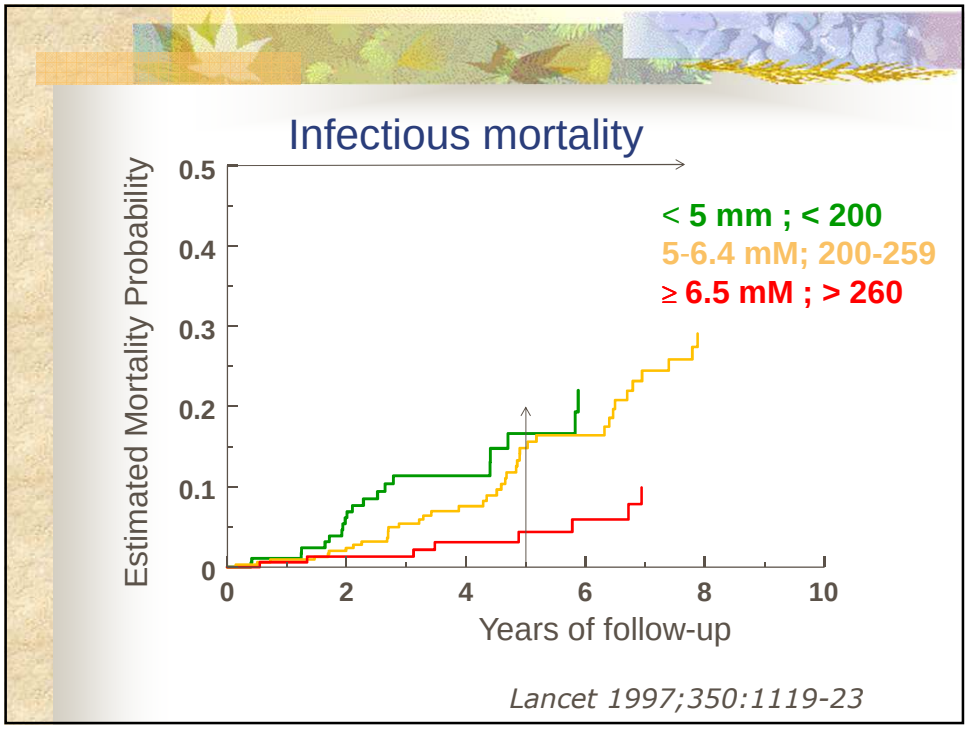

Cardiovascular mortality
Estimated Mortality Probability
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Years of follow-up
< 5 mM; < 200
5.0-6.4 mM; 200-259
≥ 6.5 mmol/L; > 260
Lancet 1997;350:1119-23


Infectious mortality
Estimated Mortality Probability
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
Years of follow-up
< 5 mm ; < 200
5-6.4 mM; 200-259
≥ 6.5 mM ; > 260
Lancet 1997;350:1119-23

Very Old Persons (85+) & cholesterol Conclusions

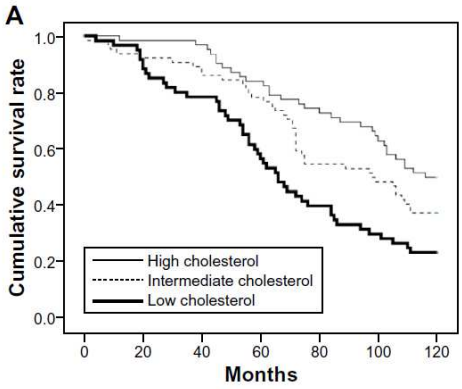
- High mortality risk (90% at 10 years)
- CVD is the first cause of mortality
- total chol. is not a risk factor for CV death
- high total chol. → increased survival !

  + 1 mM chol = - 15 % in mortality (RR 0.85 ; 0.79-0.91)
- low total chol. → increased risk of death due to infection or cancer or …

Lancet 1997;350:1119-23

Serum total cholesterol and 10-year mortality in 85-year-old Japanese population

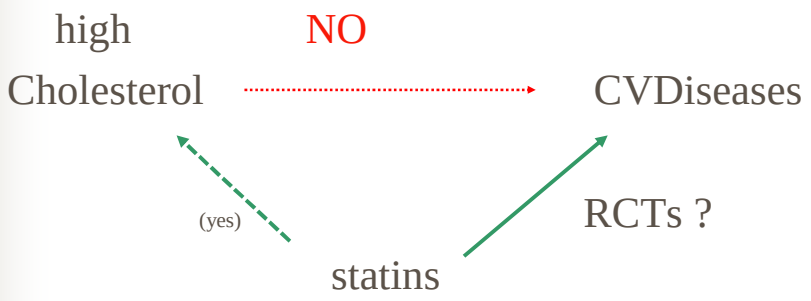
Clinical Interventions in Aging 2014:9 293–300



Serum total cholesterol and 10-year mortality in an 85-year-old Japanese population

- Introduction. Little is known about the association between total cholesterol (TC) and all-cause mortality in the elderly. Here we examined the association between TC and all-cause mortality in 207 very elderly (85-year-old) participants.
- Methods. At baseline in 2003, collection of laboratory blood tests, blood pressure (BP) and body mass index (BMI), and lifestyle questionnaires. Follow-up during the subsequent 10 years. In 2013, of the 207 participants in 2003, 70 participants had survived, 120 individuals had died, and 17 were lost to follow up. The TC values were divided into high-TC (≥ 209 mg/dL), intermediate-TC (176–208 mg/dL), and low-TC (≤ 175 mg/dL) categories. Kaplan–Meier method for survival analysis.
- Results. Both the high-TC and intermediate-TC groups survived longer than the low-TC one. The men with high TC survived longer than those with low TC, but no corresponding difference was found for the women. A multivariate Cox proportional hazards regression model, with adjustment for gender, smoking, alcohol intake, history of stroke or heart disease, serum albumin concentration, BMI, and systolic BP, revealed that the total mortality in the low-TC group was 1.7-fold higher than that in the high-TC group. Adjusted for the same factors, **mortality decreased 0.9% with each 1 mg/dL increase in the serum TC concentration** and decreased 0.8% with each 1 mg/dL increase in the serum (low-density lipoprotein) LDL-cholesterol (LDL-C)
- These findings suggest that low TC and low LDL-C may be independent predictors of high mortality in the very elderly.

evidence for links in OP (75+) ?



2. In OPersons (75+), how much is a statin appropriate ..?

- Classical approach (generalisation from < 75 !)
- EBM approach (efficacy & safety in 75+ : ?)
  - Question « P I/C O »
  - Search for valid sources of information:
    - Hierarchy: (Guidelines) > (MA) > **RCT** (few)
  - Critical appraisal
    - ***HPStudy, 2002*** *40-80 yrs* *70+: n=5.806*
    - ***PROSPER, 2002*** *70-82 yrs* *70+: all : n=5.804*
    - ***JUPITER, 2008*** *70-80 yrs* *70+: all: n+5.695*

3 voies de réponses, selon l'EBM

Fort peu de données chez OP

1. Etudes randomisées classiques
   - A. HPS_2002
   - A. PROSPER_2002
   - B. JUPITER_2010
2. Etude randomisée de terrain
3. Consensus STOPP/START

HPS, 2002
Heart Protection Study

P 20.536 patients, 40-80 yrs
28 % > 70 yrs : 5.806 were EP70+ (post-hoc)
at high CV risk : SPrevention, or Db2+other RF(s)

I / C Simvastatin 40 *vs.* placebo, **5 years**

O CV morbi-mortality (nf MI, Sk, CV†) ↓ 25 % (p < 0,001)

Comments

Statin is effective in 70-80 years at high risk (SPrevention or Db2)
with no differences related to gender, age (> 70 yrs), nor LDL-C !

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. **Lancet** 2002;360:7

PROSPER, 2002
Prospective Study of Pravastatin in the Elderly at Risk

P 5.804 pts (51% women), aged 70-82 yrs
mean 75 yrs → all were EP70+ (n=5.804)
SPrev. (n=2500) or High risk PPrev. (n=3300)

I / C 40 mg pravastatin 40 *vs.* placebo, 3.2 years

O: CV morbi-morta (nf MI, Sk, CV†) ↓ 15% overall (p=0,01)
CAD deaths ↓ ; non-fatal MI ↓ ; new cancer ↑

Comments (*no effect on MMSE*)

Not effective in Primary Prevention	+ in SPrev.
nor in women	+ in men
Little effect if HDL-C > 50	+ if low HDL-C
No effect on stroke in SP	and for CAD only

J Shepherd et al. – Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. **Lancet** 2002;360:1623

PROSPER [*Lancet* 2002;360:1623]

P: 5.804 pts, âge 70-82 ans (µ:75 ans; ♀ 51%)
HRCV, en **PCV2nd** (57%)
ou en **PCV1re** (43%)

I/C: pravastatine 40 *vs.* placebo, 3.2 ans

O:	Evénement	Fréquences/an	RRR (p-value)	NST/an
	IM, AVC, †CV	16.2 *vs.* 14.1	15% (0,01)	48
	PCV2nd	**21.7 *vs.* 17.4**	**22% (SS)**	**23**
	PCV1re	12.1 *vs.* 11.4	6% (NS)	"143"

mes commentaires: ***une statine*** *chez les PAgées 70+*
en PCV 2nd *avec haut risque CV (22%/an)* ***est utile*** *[surtout chez ♂ , HDL-C<45]*
en PCV 1re *avec haut risque CV (12%/an)* ***est inutile***

JUPITER Analyse des 70+ [*Ann Int Med* 2010; 152: 488-96]

P: 5.695 PA en **PCV1re**
LDL<130 et CRP>0.2 (µ:74 ans; ♀ 52%)

I/C: rosuvastatine 20 vs. placebo, ~ 4 ans

O:	Evénement	Fréquences/an	RRR (p-value)	NST/an
	IM, AVC, †tot	2.11 vs. 3.04 %	30% (0.001)	107
	IMyocarde	0.27 vs. 0.50 %	45% (0.05)	437
	AVCérébral	0.35 vs. 0.64 %	45% (0.02)	344
	†CV	0.34 vs. 0.41%	27% (0.53)	x
	IM, AVC, †CV	0.96 *vs.* 1.55 %	38%	"169"

mes commentaires: ***une statine*** *chez des PAgées 70+*
en PCV 1re *avec risque CV moyen (1.5 %/an)* ***n'est utile que****...*
modérément (NNT=169); et dans certains sous-groupes (SPMétab, HTA, Obésité)

Etude randomisée de terrain, DEBATE (Finlande) [Am Heart J, 2006; 152: 585-92]

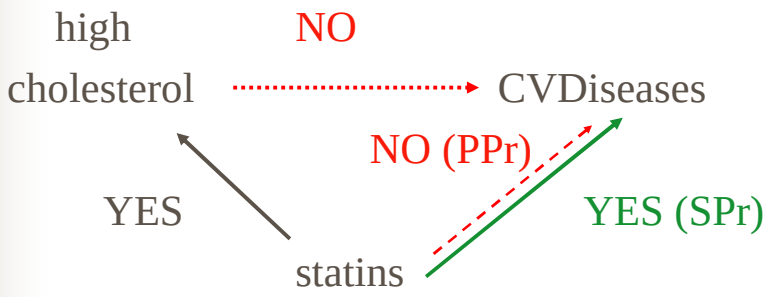
PCV 2nd chez des patients 75+ après infarctus

- ***P**atients*: *n=400, entre 75 et 90 ans*
  - *Antécédent d'infarctus*
  - *Recrutés dans la population générale*
- ***I**ntervention*: *tous les ttts recommandés*
- ***C**ontrôle*: *ttts usuels*
- ***O**utcomes*:
  - *Atteinte des cibles :* *OK (TAs, LDL-C, …)*
  - *Diminution des acc.CV:* *KO*
    - *Décès non-modifiés (18 vs. 17%) à 3.4 ans !*
    - *Délai non-modifié jusqu'à l'accident CV !*

Statins: clinical efficacy according to age (decades)

	HPS others JUPITER	HPS PROSPER JUPITER	(-)
	60 – 69 yrs	70 – 79 yrs	> 80 yrs
Secondary Prevention	+ , +	+ , +	?
Primary Prevention	+ , +	-- , ±	?

THoMessage =
in OP 75+, evidence for links



Consensus STOPP & START
(Prescription inappropriée)

Besoin d'un outil pertinent, pratique (rapide, simple), à jour

Initiative en Irlande :

- 2003: Situations fréquentes et importantes chez les PAgées
- 2004: Liste initiale, étude pilote
- 2006: Consensus, 18 experts
  gériatres, médecins généralistes, neuropsychiatres, pharmaciens
- 2008 : 65 & 22 critères retenus, et publiés

  STOPP: **S**creening **T**ool of **O**lder **P**eople's inappropriate **P**rescriptions

  START: **S**creening **T**ool to **A**lert doctors to **R**ight (appropriate, indicate) **T**reatments.
- 2008: études de terrain : prévalence élevée

	Primary Care	Hospital Adm.	Nursing Home
STOPP 21%	35 %	60 %	
START 23%	50 %	55 %	

STOPP & START

Études de validation

- 2008: reproductibilité
- 2008: validation rétrospective: détection des EIM
- 2008: validation prospective: Sur 600 PA, 158 (26%) ont des EIM (n=329, dont 219 ont causé ou contribué à l'Hospitalisation, parmi lesquels 150 étaient évitables dont 94 étaient détectés par STOPP)
- 2008: faisabilité : 2 minutes: Sur 50 PAgées avec 418 prescriptions, 102 critères STOPP et 47 critères START
- 2008: RCTrial n=400: nette diminution des médications « en trop » et en « trop peu », à la sortie, 3 et 6 mois
- > 2009 : impact sur l'incidence des EI, sur les coûts, …

Version.2

- …2014 : 2ème version, internationale
- > 2015 : essais cliniques européens (SENATOR, OPERAM)

Liste START, 2014

34 omissions de prescription potentiellement inappropriée

Introduction : prescription à envisager si indication, hors C-I et hors fin de vie

Section A: Cardio-vasculaire

Condition	→ Prescription
si FAuriculaire	→ anticoagulation (AVK ou NOAC)
& CI anticoag.	→ antiagrégant plaquettaire
si HTA >160/90	→ anti-hypertenseur
si ATHérosclérose	→ antiagrégant plaquettaire
	→ statine si âge < 85 ans et EV > 1 an
si ICardiaque systo.	→ IEC
si ICard. systo stable	→ β-bloquant
si maladie coronaire	→ IEC
si cardioϖ ischémique	→ β-bloquant

Liste STOPP, 2014

84 critères de prescription potentiellement inappropriée

Section A: Indication de prescription

A1. pas d'indication: statine/aspirine en PPrimaire, IPP sans RGO, ..
A2. durée trop longue
A3. duplication de classe (BBq, IEC, AINS, BZD, …)

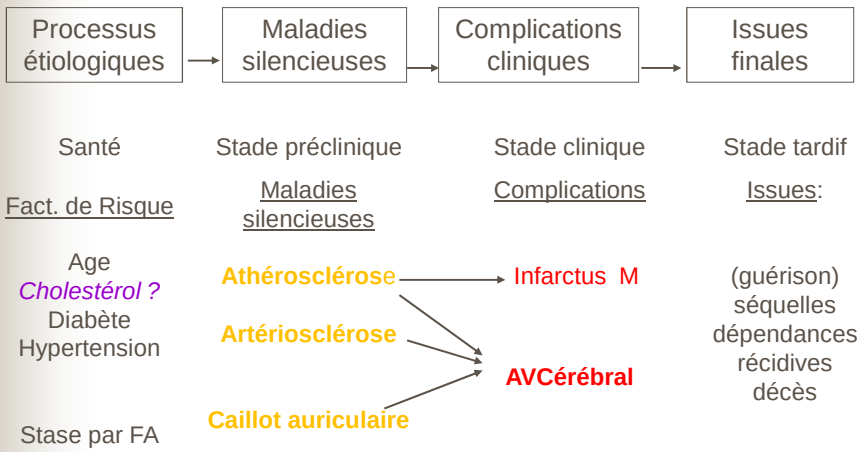
Section B: Cardio-vasculaire

Médicament	Critères (situations à risque)
Digoxine	ICard « diasto »; *>125 µg/j si FGlom <50ml/min*
Diltiaz/Verap.	ICardiaque NYHA classe III ou IV
B-bloquant	Vérap/diltiaz; FC<50; *BPCO; Db2 avec hypo*
Amiodarone	1ère ligne pour tachycardie SV
Diur. Anse	1ère ligne pour HTA
Thiazide	OMI périphériques, goutte, Na+, K+, Ca++
IEC/ARAII	hyperK+
Aldactone	IEC/ARAII, sans suivi K+
Act° centrale	(sauf si intolérances aux autres classes)
Vasodilatat.	Hypotension orthostatique objectivée

Statine, commentaires

STOPP	START
Pas d'indication : *PCV 2nd et « fin de vie »* *PCV 1re (exceptions…)*	***prescription si PCV 2de*** ***si EVie > 1 an*** ***et si âge < 85 ans***
Etudes: n=2 PROSPER_PP; JUPITER	Etude : n=1 : PROSPER_PS
410 PAgés (CUSLuc, 2010) ***statine**: 96 / 410 (23%)* *versus* en PCV1re: 47 / 260 = STOPP (dont âge > 85 ans: 15) en PCV2de : 49 / 150 dont âge > 85 ans : peu dont EV<1 an: ?	âge 85±5 ans, 8± 4 médicaments/jour ***pas de statine**: 314 / 410 (77%)* en PCV1re: 213 / 260 : OK en PCV2de: 101 / 150 dont âge < 85 ans : 57 = START dont EV<1 an: ?

Maladies CV chez les PAgées (75+)



PCV & PAgées (75+)

	STOPP car « futile »	START car « utile »
Statine	PCV1re PCV2nd & âge > 85 ans & EV<1 an	 PCV2nd & âge < 85 ans & EV>1 an (& indépendance fct°)
anti-HTA	Chute & hTAO	**HTA (≥ 160/90 mmHg)**
Anticoagulation	FA avec risque AVC < risque HICranienne	**FA avec risque AVC > risque HICranienne/décès**